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Applications of biocatalytic arene *ipso*,*ortho cis*-dihydroxylation in synthesis

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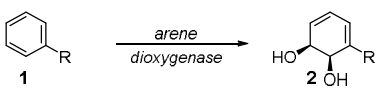
The dearomatising dihydroxylation of aromatic molecules mediated by arene dioxygenase enzymes can provide cyclohexadiene-diols that are versatile starting materials for organic synthesis. Whereas oxidation of a substituted arene to give its *ortho*,*meta*-dihydrodiol has been demonstrated for numerous substrates and dioxygenases, formation of *ipso*,*ortho*-dihydrodiols has historically been underutilised in comparison. This feature article presents a chronological account of reported uses of such diols.

Introduction

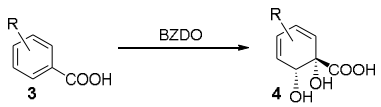
The first example of the dearomatising dihydroxylation of an aromatic ring by a microorganism was reported by Gibson in 1968.[1] Some two decades later, it was recognised that the cyclohexadiene diols formed in this manner were useful starting materials for synthesis by virtue of their densely-packed, differentiated functionality. Large-scale production and use of these arene-derived diols has become established methodology and many are now commercially available; the field at large has been the subject of several excellent reviews.[2]

If the aromatic substrate is substituted (i.e. all cases other than benzene), multiple isomeric diol products can be envisaged. In fact, however, such bio-oxidations are highly selective and a widely-applicable predictive model has been developed by Boyd and co-workers.[3] As shown in Scheme 1, the diol **2** derived from oxidation at the *ortho*- and *meta*-positions of substrate **1** is the sole product. Furthermore, in most cases, **2** is formed as a single enantiomer.[4]



Scheme 1. Boyd's model for regio- and enantioselectivity of dihydroxylation.

The selectivity shown above is conserved across a large number of substrates and dioxygenases, for example toluene dioxygenase (TDO), naphthalene dioxygenase (NDO) and biphenyl dioxygenase (BPDO). However, exceptions to this predictive model are known. Organisms expressing benzoate dioxygenase (BZDO) enzymes dihydroxylate benzoic acids in a process that proceeds not only with different regioselectivity but also the opposite absolute sense of enantioinduction to that shown in Scheme 1. In these cases, the diol **4** derived from oxidation at the *ipso*- and *ortho*-positions of substrate **3** is isolated.



Scheme 2. Alternative selectivity of benzoate dioxygenase.

Diols of type **4** are potentially highly versatile chiral pool starting materials and many transformations of these building blocks can be proposed (Figure 1). Although diols of type **4** have been known since 1971, reports on their production and use have been very scarce until recently. There has been an upsurge of interest in the last three to four years and it is therefore appropriate that this rapidly expanding field be reviewed. Many (but not all) of the reactions depicted in Figure 1 have in fact been reported and the purpose of the current review is to present a comprehensive treatment of the use of diols of type **4** in synthesis to date.

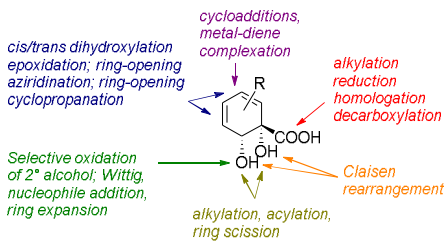
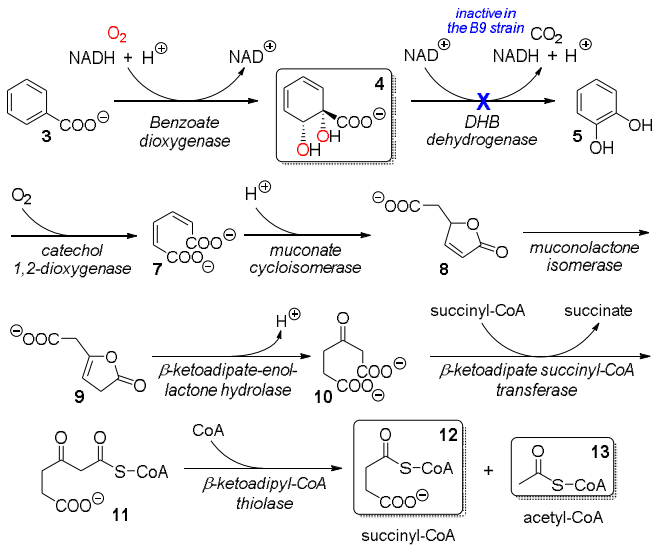


Figure 1. Possible transformations of diols of type **4**.

Initial isolation and substrate scope

The parent *ipso*,*ortho* benzoate dihydrodiol (**4**, R = H) was first reported in 1971 by Reiner and Hegeman.[5] The prokaryote *Alcaligenes eutrophus* (now known as *Ralstonia eutropha*) was known to be able to metabolise benzoate *via* catechol and the β-ketoadipate pathway. Benzoate dihydrodiol **4** is the first

intermediate in this pathway,[6] but in the wild-type organism it is only a fleeting metabolic intermediate and never accumulates to a synthetically useful concentration. The B9 mutant strain of *R. eutropha* expresses BZDO able to mediate the formation of **4**, but it possesses a lesion which renders the second enzyme in the pathway (DHB dehydrogenase) inactive.[7] Accordingly, **4** was prepared by fermentation of benzoate with the B9 strain. Isotopic labelling studies demonstrated that both hydroxyl oxygens in **4** are incorporated from the same oxygen molecule (Scheme 3).



Scheme 3. The β-ketoadipate pathway (also known as the *ortho* pathway) for metabolism of benzoate.

Reiner and Hegeman characterised **4** spectroscopically and inferred the *cis* relationship of the vicinal diol by means of chemical correlation, although the absolute configuration remained undetermined. They also deduced the positions of hydroxylation to be *ipso* and *ortho* by considering the products formed when **4** undergoes decomposition by rearomatisation at 45 °C or above, i.e. phenol and salicylic acid.

Early uses in synthesis – cycloadditions and other diene functionalisations.

In 1986, Ribbons *et al.* demonstrated that *Pseudomonas putida* U103 was capable of accumulating *cis* diol **4** (R = H) in the same fashion as *R. eutropha* B9.[8] It was not until 1995, however, that *cis* diol **4** produced in this way was exploited for synthetic ends, by Widdowson and co-workers in collaboration with Ribbons.[9] Comparison of $[\alpha]_D$ values showed that the material produced by the two organisms was the same enantiomer, but the absolute configuration remained undetermined. Widdowson and Ribbons addressed this through the synthesis of a derivative **14** containing a heavy atom and its crystallographic analysis, establishing the (1*S*,2*R*) configuration for the first time (Figure 3).

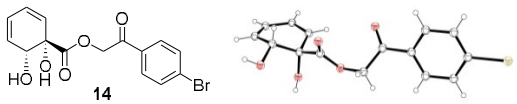
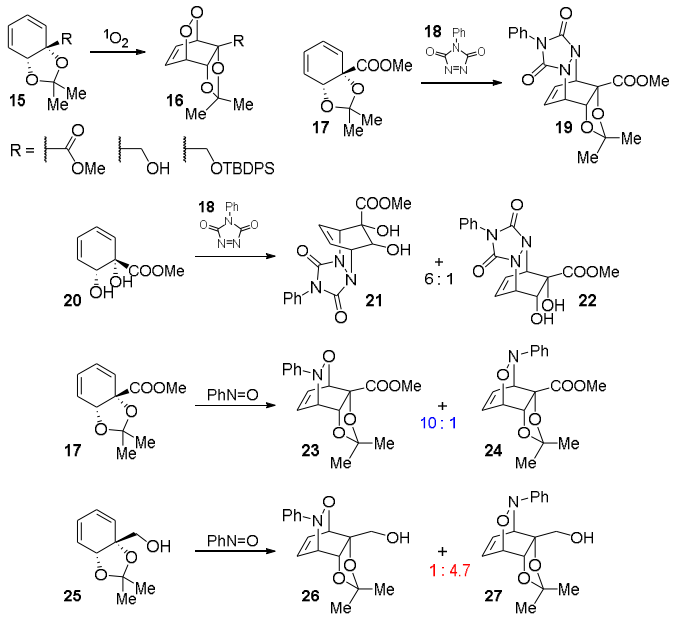


Figure 3. Confirmation of absolute stereochemistry of a derivative of **4**.

Widdowson's report further described a variety of [4+2] cycloadditions employing derivatives of **4** as the dienes. For the more common arene *ortho,meta* diols of type **2**, many such reactions had already been reported and a trend in the regioselectivity had been discerned: substrates with an unprotected diol undergo cycloaddition at the diene face *syn* to the diol, whereas when the diol is protected as a ketal, cycloaddition occurs at the *anti* face. In such dienes of type **2**, the substituent R is in the plane of the diene and would not be expected to influence the regioselectivity of cycloaddition. In contrast, dienes derived from **4** possess a substituent at the C1 quaternary centre which is oriented over the diene face *anti* to the diol. The effect of this on the regioselectivity of various cycloadditions was determined (Scheme 4).



Scheme 4. Cycloadditions reported by Widdowson *et al.*

With acetonide protected substrates **15**, singlet oxygen cycloaddition was found to proceed at the face *anti* to the acetonide, giving **16** as the sole product, even when the quaternary centre bears a bulky –CH_2OTBDPS group. Similarly, treatment of acetonide **17** with *N*-phenylurazole **18** gave adduct **19** only. In contrast, free diol **20** gave adduct **21** (in which dienophile and diol are *syn*) as the major product. Treatment of acetonide **17** with a non-symmetrical heterodienophile, nitrosobenzene, gave addition exclusively *anti* to the acetonide, but a mixture of regioisomers **23** and **24** was obtained; the adduct **23** in which the *N*-phenyl substituent is distal to the ester was the major product. Reaction of free diol **20** with nitrosobenzene gave all four possible regioisomers (not

shown). Interestingly, when an acetonide with a reduced side chain, **25**, was used in place of **17** in the nitrosobenzene cycloaddition, regioselectivity was reversed, with the major product **27** being the one in which the *N*-phenyl substituent and the ester are proximal.

In 2001, Myers and co-workers reported the synthesis of a library of derivatives of **4**, demonstrating that each position on the ring may be functionalised selectively (Figure 4).[10] While selective protection of the secondary alcohol in **4** is straightforward (e.g. **28** and **29**) protection of the tertiary alcohol necessitated an indirect route via **30**, which upon desilylation gave **31**. This in turn underwent oxidation to cyclohexadienone **32** (a transformation which is low-yielding for the unprotected diol **20**). Selective epoxidations to **33** and **34** were demonstrated, along with ring openings to diastereomeric *trans* diols **35** and **36**; *cis* diols were accessible by OsO_4 catalysed dihydroxylation, e.g. **37**. Intramolecular epoxide opening was shown to afford lactone **38** and acetalisation of the diol in **33** (a highly acid-sensitive substrate) was achieved under neutral conditions to give **39** (*R*/*S* 2:3). Bromolactonisation of **20** gave β-lactone **40**, which underwent attack by methoxide to give **41**. Attempts to access enones such as **42** through rearrangement of C3,C4 epoxides such as **33** were unsuccessful. Instead, an unexpected vinylogous Payne rearrangement was discovered: methylation of **33** followed by treatment with *tert*-butyldimethylsilyl triflate led to formation of trisubstituted epoxide **43** in good yield.

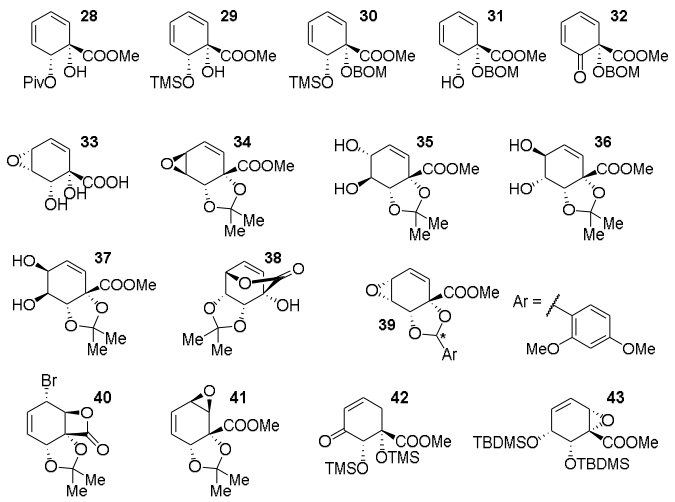
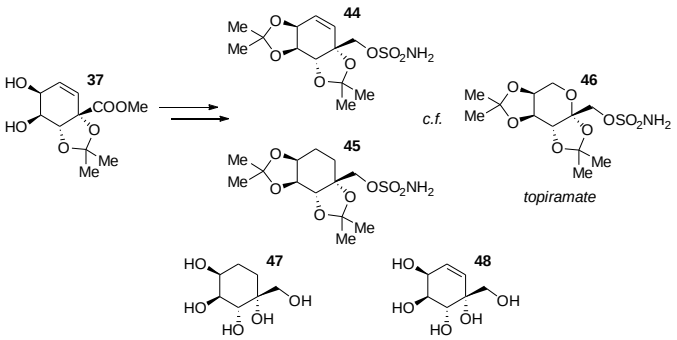


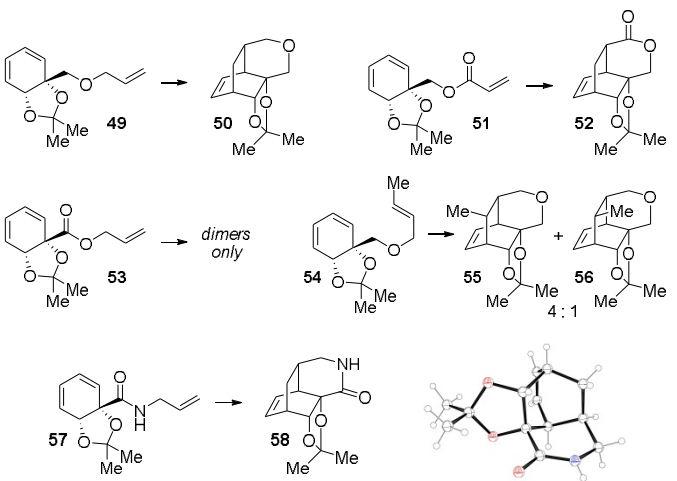
Figure 4. Chirons derived from **4** by Myers *et al*.

The Myers group also reported a modified protocol for the fermentation of benzoate to produce **4** which was amenable to large-scale application. By this method, 270g of **4** was produced in a single batch. The authors speculated that the novelty of the building blocks shown above in conjunction with large-scale access to the starting material would enhance interest in the use of **4**. Indeed, in 2004, Parker and co-workers at Johnson & Johnson reported using **37** to access carbocyclic analogues of the anticonvulsant agent topiramate **46**, as well as carba-β-L-fructopyranose **47** and a C-substituted conduritol **48** (Scheme 5.)[11]



Scheme 5. Johnson & Johnson synthesis of topriamate analogues.

Also in 2004, Mihovilovic and co-workers reported on intramolecular cycloadditions of derivatives of **4** bearing a tethered dienophile (Scheme 6).[12] Cyclisation of **49** to **50** was high yielding, but introduction of an sp^2 centre in the tether retarded reaction: **51** gave **52** only under forcing conditions of microwave acceleration and **53** did not undergo intramolecular cyclisation at all. Interestingly, disubstituted dienophile **54** gave a mixture of diastereomeric products **55** and **56**. Finally, in contrast to ester **53**, amide **57** was able to cyclise to **58**, albeit only under forcing conditions and in low yield; the structure of the cycloadduct **58** was secured by x-ray crystallography. This work demonstrated the possibility of rapidly accessing complex polycyclic architectures from **4**.

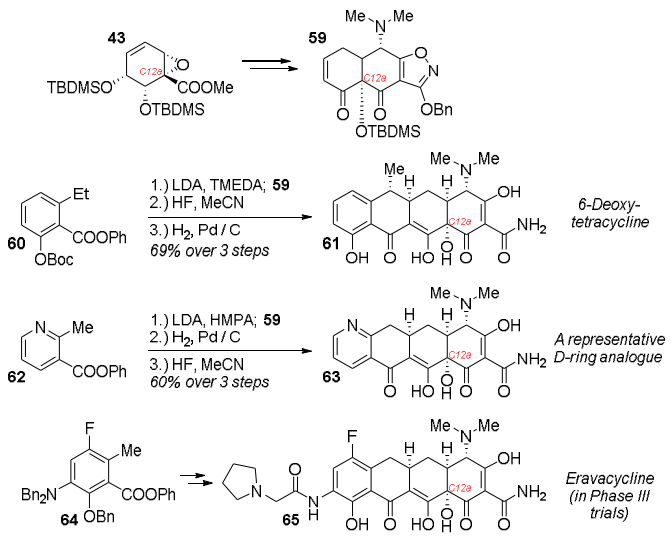


Scheme 6. IMDA reactions of derivatives of **4**.

First total synthesis

In 2005, Myers and co-workers reported the first use of **4** in complex natural product total synthesis.[13] From their previously reported building block **43**, tricyclic diketone **59** was accessible in a further 7 steps (10% overall yield from benzoate, Scheme 7). Diketone **59** serves as a common precursor to the

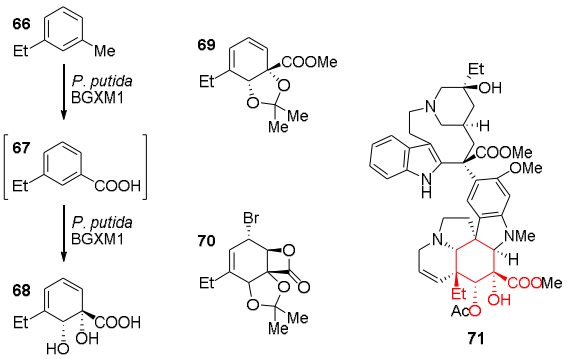
tetracycline AB-ring system and may be coupled with D-ring precursors such as **60** by a Michael–Dieckmann cascade cyclisation that forms the C-ring. Thus, after deprotection, the natural product (–)-6-deoxytetracycline **61** is accessible in 14 steps and 7.0% overall yield from benzoate. Several points about the synthesis are noteworthy. The yield represents an improvement of orders of magnitude over the yields for all previously reported total syntheses of tetracyclines. Thus, for the first time, novel tetracycline analogues became accessible in useful quantities; union of **62** with **59** to access **63** is a representative example. Secondly, previous total syntheses of tetracyclines had been bedevilled by the difficulty of installing the C12a tertiary alcohol at a late stage.[14c] The Myers approach is conceptually distinct in that the C12a hydroxyl group is installed in the very first step, *i.e.* it is the hydroxyl group deriving from the microbial *ipso* hydroxylation. Finally, apart from the C12a stereocentre, all other stereocentres in the final tetracyclines are set under substrate control. Thus, all the stereochemical information in the final products may be considered ultimately to be of enzymatic origin.



Scheme 7. Myers' synthesis of tetracycline antibiotics.

In the years following the Myers group's initial disclosure, the methodology has been extended and improved to allow for the preparation of a greater diversity of novel tetracycline analogues.[14] This has culminated in the development of eravacycline **65** (accessed from **59** and **64**) by Tetraphase pharmaceuticals.[15] Eravacycline is indicated for treatment of multidrug-resistant infections and is currently in phase III trials.

Also in 2005, Banwell and co-workers reported the production of **68**, a substituted variant of **4** (R = 3-ethyl).[16] This was produced not from *meta*-ethylbenzoic acid **67**, but instead from *meta*-ethyltoluene **66**, using *Pseudomonas putida* BGXM1. This organism expresses enzymes capable of oxidising toluene to benzoic acid, as well as toluate dioxygenase which catalyses the production of **68**. Thus, **67** is metabolically generated *in situ* and **68** accumulates since the organism does not express a functioning toluate diol dehydrogenase (*c.f.* Scheme 3). Simple transformations of **68** were demonstrated (Scheme 8), e.g. formation of acetonide **69** and β-lactone **70** (*c.f.* formation of **40**, Figure 4) and the absolute configuration of **68** was confirmed through formation of a heavy atom derivative, analogous with **14**. The relevance of **68** to total synthesis lies in its potential utility as a building block for the synthesis of vinblastine **71**.



Scheme 8. An alkyl-substituted benzoate *ipso,ortho* diol.

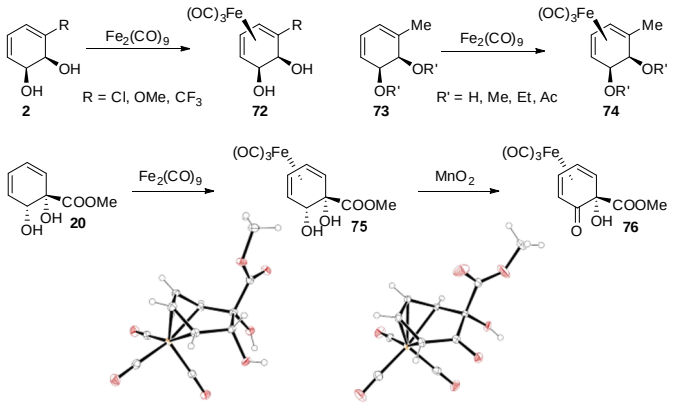
Production with a recombinant organism

In 2008, Chen and co-workers reported the production of a recombinant strain of *Pseudomonas putida*, KTSY01 (pSYM01) expressing benzoate dioxygenase and able to effect formation of **4** on a 59g scale.[17] This organism is engineered to overexpress the *benABC* genes from *Pseudomonas putida* KT2442 that encode benzoate dioxygenase, but lacks the *benD* gene that encodes the DHB dehydrogenase responsible for the further metabolism of **4** (*c.f.* Scheme 3). A potential advantage of using this organism for production of **4** is that it is not susceptible to the unwanted formation of revertants. In contrast, use of organisms such as *Ralstonia eutropha* B9 where inactivation of DHB dehydrogenase was achieved through random mutagenesis entails a risk of spontaneous reactivation, and hence consumption of **4** in the fermentation medium.

Organometallic chemistry

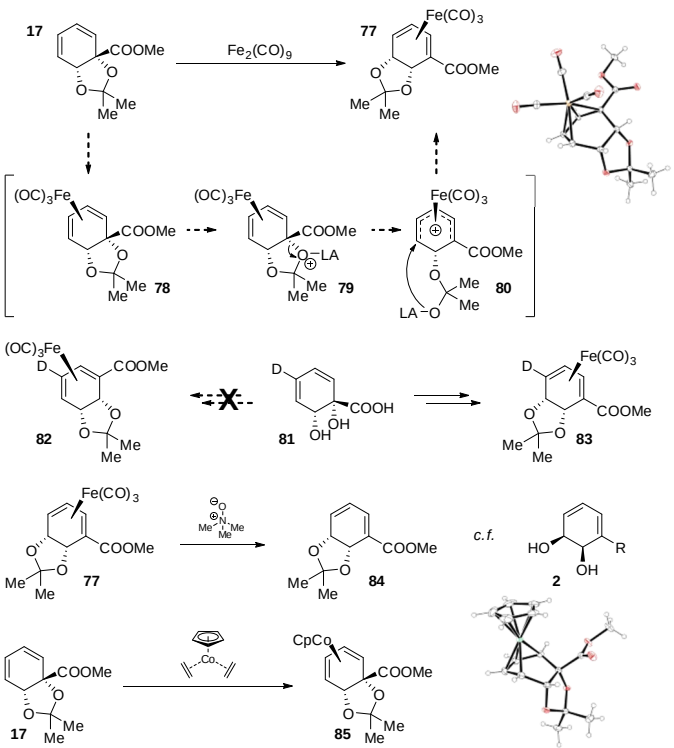
The formation of tricarbonyliron(0) complexes of arene *ortho,meta* diols of type **2** was known methodology[18] and in 2010 we extended this to an arene *ipso,ortho* diol for the first time (Scheme 9). Formation of these [η^4] complexes from dienes of type **2** was known to be selective for the isomers in which the metal is *endo* with respect to the diol, i.e. **72** and **74**. This had been rationalised in terms of an incoming 16 valence-electron $Fe(CO)_4$ fragment coordinating to the Lewis basic oxygen functionality before migrating to the diene. By this argument, it was not clear at the outset which face of diene **20** would be favoured in the complexation, since due to the quaternary centre **20** presents Lewis basic functionality on both sides of the ring. In the event, the isomer **75** with the metal *endo* to the diol was formed exclusively and the structure was secured by crystallography. The impetus for introducing the

tricarbonyliron group had been to protect the diene functionality in **20**. That tricarbonyliron was effective in this regard was demonstrated by clean oxidation of **75** to complexed cyclohexadienone **76**. This transformation is low-yielding for unprotected **20** and necessitated benzyloxymethyl protection of the tertiary hydroxyl as **31** (Figure 4) when this transformation was examined by Myers. Dimerisation of cyclohexadienones is precedented and in the case of **32** reportedly proceeded with $t_{1/2}$ ≈ 4 h (0.6 M, 23 °C, $CDCl_3$). In contrast **76** was stable indefinitely.



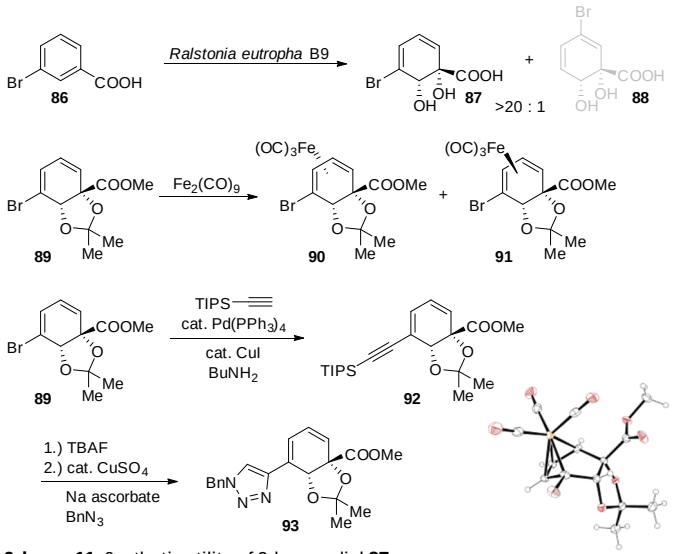
Scheme 9. Tricarbonyliron(0) complexes of arene *cis* diols.

In 2011, in an attempt to access a complex of **4** bearing the metal on the upper face, we subjected acetonide ester **17** to the same reaction conditions (Scheme 10), in the expectation that protection of the diol as an acetonide would attenuate its directing ability. In the event, a product was isolated in which the iron was indeed coordinated to the upper diene face, but in which a rearrangement had occurred, conjugating the ester to the diene and giving **77**.[20] We rationalise this result through initial formation of the expected product **78** and its subsequent co-ordination of an unknown Lewis acidic species to give **79**. C–O bond scission would then afford cationic cyclohexadienyl complex **80**. It is known that $[\eta^5]^+$ complexes such as **80** undergo nucleophilic attack at the termini of the dienyl system and the acetonide in **80** constitutes a tethered nucleophile. Its recombination at the position ω- to the ester[21] and decomplexation of the Lewis acid would afford the observed product, **77**. In support of this mechanism, we observed that selectively deuterated *ipso,ortho* diol **81** gave rise to **83** and not the isomeric **82**, thereby demonstrating that the rearrangement involves "clockwise" acetonide migration and not "anticlockwise" ester migration. Decomplexation of **77** gave **84**, which is significant insofar as it is the opposite enantiomer of the arene *ortho,meta* derivative that would be obtained by direct arene biotransformation (*c.f.* Scheme 1). Interestingly, formation of an isolobal cobalt cyclopentadienyl complex from **17** did not result in any such acetonide migration and instead gave **85**.[22]



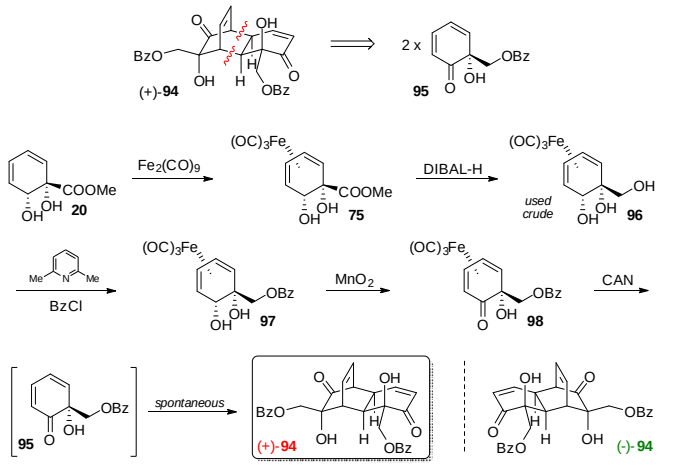
Scheme 10. Acetonide migration allows access to antipodal *ortho,meta* diols.

The metabolism of substituted benzoates by *Ralstonia eutropha* B9 had been reported (*vide infra*) and we examined the feasibility of producing arene *ipso,ortho cis* diols from *meta*-bromobenzoate in synthetically useful quantities. Metabolism of a *meta*-substituted benzoate could potentially give rise to two isomeric products (Scheme 11). In the event, we found formation of 3-bromo isomer **87** to be greatly favoured over 5-bromo isomer **88**.[23] Although turnover of **86** was much lower than for unsubstituted benzoate, sufficient quantities were nevertheless produced to demonstrate its utility in synthesis. Protection of **87** as acetonide ester **89** and complexation with iron tricarbonyl afforded facial isomers **90** and **91**, but no rearrangement to a product analogous with **77** was observed. Various transformations of **89** were demonstrated in order to showcase the versatility of the bromo substituent as a handle for further functionalisation – a representative example is shown in Scheme 11, i.e. a Sonogashira coupling followed by Huisgen copper catalysed azide–acetylene cycloaddition to access triazole derivative **93**.



Scheme 11. Synthetic utility of 3-bromo diol **87**.

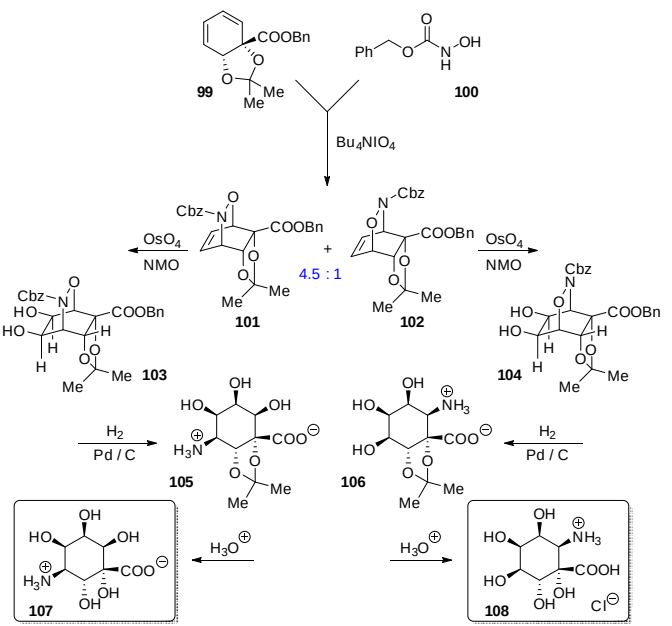
The organoiron chemistry described above has found application in total synthesis. Also in 2011, we described a route to (+)-grandifloracin (+)-**94**, a polyoxygenated cyclohexene derivative isolated from species in the genus *Uvaria*. The structure is a dimer deriving from Diels–Alder reaction of cyclohexadienone **95** in a remarkably regio- and stereoselective reaction.[24] Accordingly, it proved possible to adapt the methodology shown in Scheme 9 for a concise synthesis of (+)-**94**.[25] Complex **75** may be reduced to triol **96**, which is then benzoylated to give **97**. Chemoselective oxidations were then required: manganese dioxide had been established as the oxidant of choice for oxidising the secondary alcohol without cleaving the metal fragment, in this case giving **98**. A different oxidant, in this case cerium ammonium nitrate, deprotected the diene to give **95**, which underwent facile dimerisation to give (+)-**94**. At the time this work was carried out, grandifloracin had been isolated from Nature as a single enantiomer of unknown absolute configuration.[26] Our work described the synthesis of material of known absolute configuration, but when its optical rotation was compared with that reported for the natural material, we found that our material (of structure (+)-**94**) had a positive rotation, whereas the natural material had a negative rotation and hence structure (–)-**94**. On this basis we stated that we had synthesised the "non-natural enantiomer of grandifloracin". *However*, a year after our report, Awale and co-workers reported the isolation of (+)-**94** from a different species of the same genus.[27] Thus, both enantiomers of grandifloracin are in fact found in Nature and our statement that we had synthesised "the non-natural enantiomer" was in fact incorrect. Furthermore, Awale reported that the (+) enantiomer is an "anti-austerity" agent, *i.e.* shows preferential antiproliferative activity against pancreatic cancer cell lines in a nutrient-deprived condition.



Scheme 12. Total synthesis of (+)-grandifloracin from **4**.

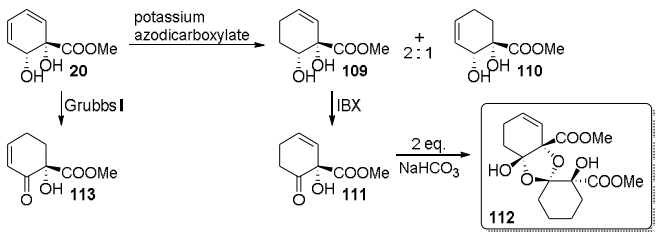
Oxygenation

In the same year, we described the synthesis of "inosamino acids", amino acid-inositol hybrid structures accessed from **4**.[28] An acylnitroso dienophile (generated *in situ* by periodate oxidation of **100**) reacted with benzyl ester **99** to give separable isomeric adducts **101** and **102** (Scheme 13). The major product (**101**) was that in which the benzyl ester was distal to the Cbz group, analogous with formation of **23** over **24** (Scheme 4). Additional oxygenation was introduced by stereoselective dihydroxylation of the residual olefin in **101** and **102**, giving **103** and **104** respectively. Hydrogenolysis of these diols effected multiple reductive operations in one pot; this was followed by deprotection with aqueous acid to give inosaminoacids **107** and **108**. These inosaminoacids possess six contiguous stereocentres, including the quaternary centre, and were accessed in just seven steps from benzoate, highlighting the usefulness of **4** for the rapid introduction of complexity.



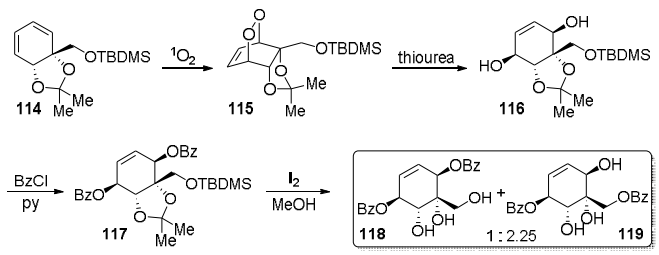
Scheme 13. Synthesis of "Inosaminoacids"

Another example in 2011 of the synthesis of a highly oxygenated material from **4** was the total synthesis of (–)-idesolide **112** reported by Hudlický *et al.*[29] This is another dimeric natural product, formed from a ketone, but in this instance the diene motif was reduced beforehand (Scheme 14). Reduction of one of the two olefins in **20** was effected with potassium azodicarboxylate, giving a 2:1 ratio favouring the desired isomer **109**. This in turn was oxidised to ketone **111**, which underwent base-mediated dimerisation to (–)-idesolide **112**. Another noteworthy transformation reported by the group was the direct isomerisation of **20** to enone **113** using Grubbs' 1st generation Ru metathesis catalyst.



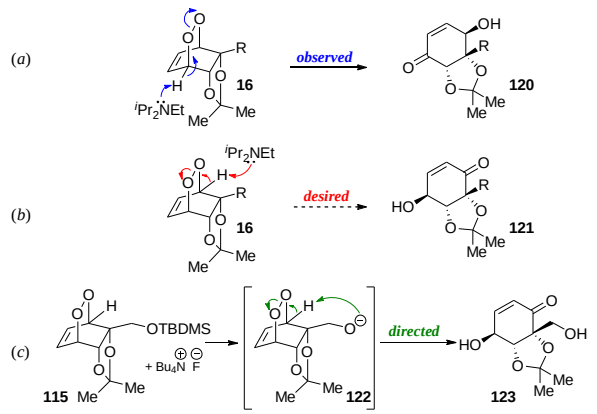
Scheme 14. Total synthesis of (–)-idesolide by Hudlický and co-workers

In 2012, we returned to the polyoxygenated cyclohexene family of natural products, of which there are numerous monomeric members in both enantiomeric series in addition to the dimer grandifloracin **94**. The key transformation to access both the zeylenol and zeylenone families of natural product was singlet oxygen cycloaddition, which transformed diene **114** into endoperoxide **115**. From this key intermediate many members of these families were accessed.[30] A representative example is shown in Scheme 15, whereby reductive O–O bond cleavage with thiourea gave diol **116**. Straightforward benzoylation and global deprotection gave uvaribonol A **118** as well as the parent (+)-zeylenol **119** by benzoyl migration.



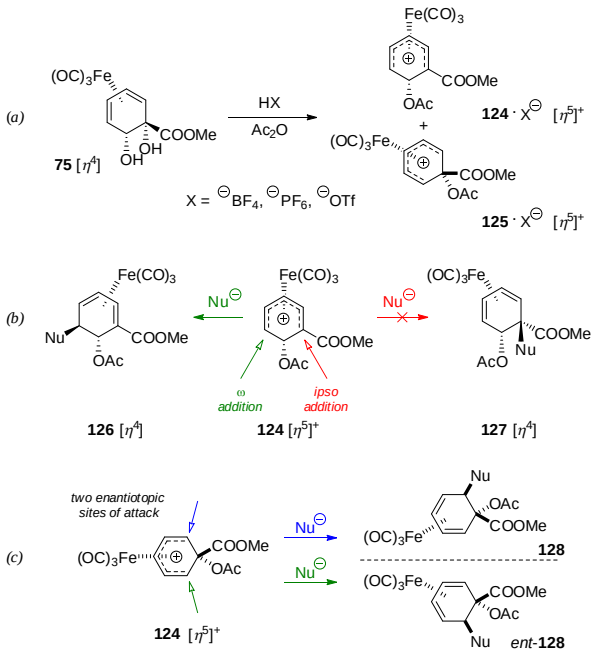
Scheme 15. Total synthesis of zeylenols

Whereas access to the zeylenols required a reductive transformation of endoperoxide **115**, access to the more highly oxygenated zeylenones ought to be possible from **115** by a redox-neutral process. The γ-hydroxy-α,β-unsaturated ketone motif in the zeylenones could conceivably be accessed from the endoperoxide by a Kornblum–DeLaMare rearrangement.[31] A variety of endoperoxides of general structure **16** underwent regioselective Kornblum–DeLaMare fragmentation with Hünig's base to give the corresponding γ-hydroxy enones **120** (Scheme 16a). This regioselectivity is rationalised in terms of the base abstracting the less sterically hindered of the bridgehead protons in endoperoxide **16**. Unfortunately the desired zeylenone skeleton has the opposite regiochemistry, exemplified by **121** (Scheme 16b). Such a γ-hydroxy enone isomer did eventually prove to be accessible by means of an intramolecular deprotonation: treatment of endoperoxide **115** with TBAF gave γ-hydroxy enone **123** with the correct zeylenone skeleton (Scheme 16c). We propose that the alkoxide **122** formed *in situ* by desilylation is able to effect the desired deprotonation leading to **123**.



Scheme 16. Directed Kornblum-DeLaMare fragmentation of a derivative of **4**.

In 2012 we also reported further organoiron chemistry which exploits the oxygenation in complex **75** to access a range of cyclohexadienes bearing diverse substituents and with different substitution patterns.[32] A tricarbonyliron [η^4] diene complex bearing a leaving group adjacent to the diene is able to extrude this leaving group to form the corresponding [η^5]$^+$ complex (*c.f.* Scheme 10). In the case of **75**, either of the two hydroxyl functionalities is capable of acting as the leaving group upon protonation with a Brønsted acid comprising a non-nucleophilic anion (Scheme 17a). This reaction was found to work best in acetic anhydride as solvent and proceeds with comcomitant hydroxyl acetylation. Thus, if the tertiary hydroxyl in **75** is the leaving group, [η^5]$^+$ complex **124** may be formed, whereas if the secondary hydroxyl in **75** is the leaving group, [η^5]$^+$ complex **125** would form instead. Realtime NMR monitoring of this reaction revealed that in fact both cations are formed, with **125** being the major product (≈3:1 ratio). Once formed, both of these cations are susceptible to nucleophilic attack at their diene termini. For [η^5]$^+$ complex **124**, attack ω- or *ipso*- to the ester would afford regioisomeric products **126** or **127** respectively. As discussed above, regioselectivity in such nucleophilic additions is precedented[21] and only products of type **126** are formed (Scheme 17b). For [η^5]$^+$ complex **125**, loss of the secondary hydroxyl in fact introduces a plane of symmetry, *i.e.* **125** is achiral. Thus, the two diene termini are enantiotopic and addition of any achiral nucleophile to **124** will give a product (±)-**128** as a racemic mixture.



Scheme 17. Cations accessible from complex **75**.

The cationic complexes **124** and **125** were treated with a variety of nucleophiles and the resulting adducts were demetallated to give a library of novel cyclohexadienes (Figure 5). The possibility was considered that equilibration between cations **124** and **125** (by acetoxy migration) might lead to erosion of the *e.e.* of **125** and hence of dienes such as **129**-**132** derived from it. However, comparison of a derivative of **132** with racemic material showed it still to be enantiopure. The chemistry outlined in Scheme 17 was also applied to formal syntheses of oseltamivir[33] and gabaculine.[34]

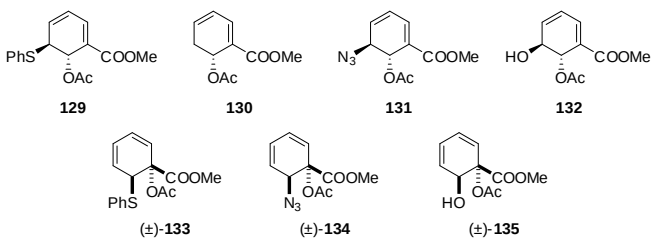
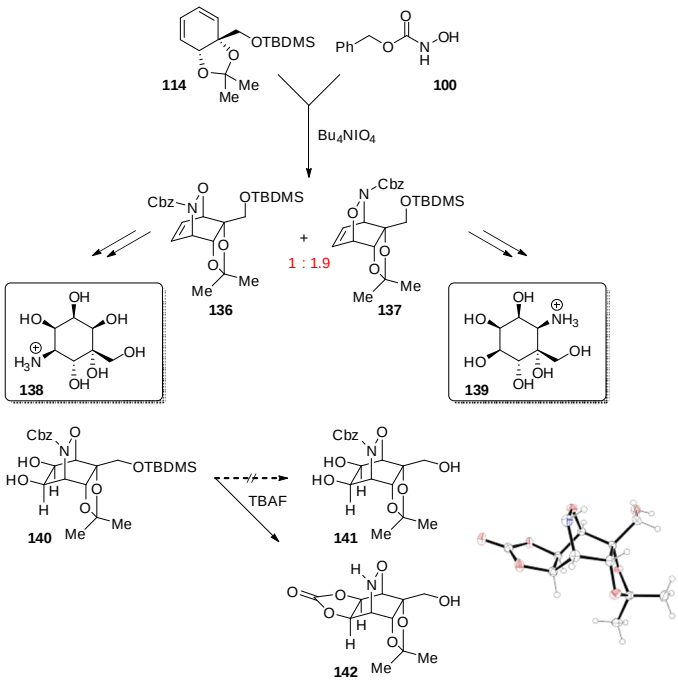


Figure 5. Access to a library of cyclohexadienes by substitution of oxygenation.

In 2013 we revisited the inosaminoacid chemistry we had described two years previously, this time targeting structures bearing a side chain in a lower oxidation state;[35] these were anticipated to have differing solubilities to the zwitterionic inosaminoacids **107**-**108** shown in Scheme 13. The chemistry bears many similarities to the previous report, but one notable difference is the reversal in regioselectivity for the acylnitroso cycloaddition when the side chain is in a lower oxidation state (Scheme 18). The isomer in which the side chain and the NCbz group are proximal, **137**, predominates over the isomer in which they are distal, **136**. This is the opposite of the selectivity depicted in Scheme 13, but in fact this regiochemical switch is precedented in Widdowson's early work (*c.f.* Scheme 4). An unexpected result during the course of this work was the formation of cyclic carbonate **142** upon exposure of diol **140** to desilylation conditions.



Scheme 18. *C*-substituted inosamines accessed from **4**.

Most recently, in 2014, we have reported an additional selection of chirons derived from **4**, this time focusing on structures possessing a saturated ring, e.g. **143**-**146** (Figure 6).[36] This report also details routes to *C*-hydroxymethyl-*muco*-inositol **147** and bis(epoxide) **148**.

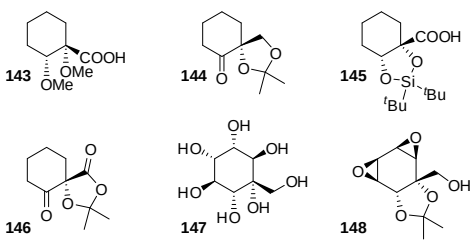
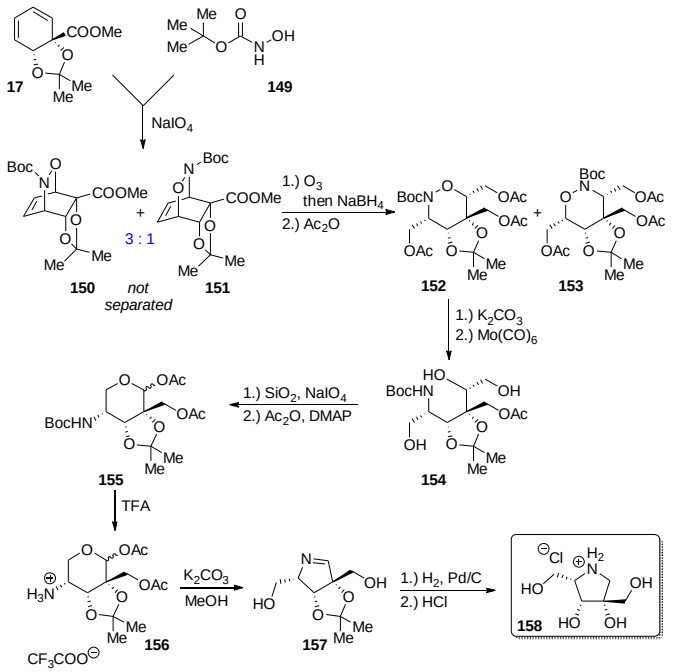


Figure 6. Chirons derived from **4** through saturation of the diene, as well as further highly oxygenated targets.

The most recent report from the Hudlický group describes the first synthesis of an iminosugar from **4**,[37] *i.e.* a structure possessing an endocyclic nitrogen, as opposed to the exocyclic nitrogens in structures **107**, **108**, **138** and **139**. Nitrogen is introduced by means of an acylnitroso cycloaddition with a different dienophile from that used in Schemes 13 and 18 and the residual alkene in **150**/**151** is cleaved by ozonolysis (Scheme 19). The N–O bond in **152** is selectively cleaved with molybdenum hexacarbonyl before one carbon is excised from the chain by periodate-mediated diol cleavage; acylation of the resultant hemiacetal gives **155**. Boc deprotection and acetate

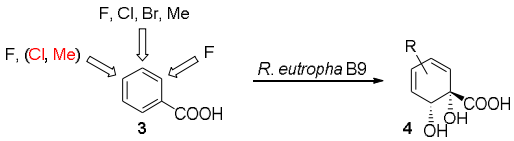
removal by methanolysis gives the free hemiacetal whose open-chain form is able to undergo cyclic imine formation to give **157**. After hydrogenolysis and removal of the ketal, the final product is isolated as its hydrochloride salt, **158**.



Scheme 19. Hudlický's synthesis of a polyhydroxylated pyrrolidine from **4**.

Future directions

The chemistry reviewed above underscores the broad range of applications in synthesis for arene *ipso,ortho* diols such as **4**. Nevertheless, there is undoubtedly great scope for further novel applications of **4** – for example, not all the transformations outlined in Figure 1 have yet been realised. In addition to transformations of the parent unsubstituted **4**, the metabolism of substituted benzoates to their *ipso,ortho* diols and their subsequent synthetic use is an obvious area ripe for exploitation, given the comparative dearth of examples (see Schemes 8 and 11). Reiner & Hegeman's initial report[5] on *Ralstonia eutropha* B9 in fact also examined the susceptibility of substituted benzoates to dihydroxylation and in the ensuing decade, Knackmuss and co-workers studied this in more detail.[38] It was determined that the *meta*- position was the most tolerant of substitution, followed by the *para*- position. The *ortho*- position was the least tolerant of substitution, with only 2-fluorobenzoate being turned over (Scheme 20). The first study to quantify product formation from *meta*-substituted benzoates stated that 5-substituted diols were formed more rapidly than the corresponding 3-substituted regioisomers.[38a] However, later studies determined this statement to be incorrect for *meta*-methyl[38c] and *meta*-bromo[23] benzoates, with the 3-substitited products in fact predominating. (Note that a large number of aromatic substrates which are not substrates for BZDO from *Ralstonia eutropha* B9 have been identified[39]).



Scheme 20. Substituted benzoates as substrates (substrates in parentheses give especially slow turnover).

Formation of *ipso,ortho* diols from multiply fluorinated benzoates has been described using *Pseudomonas putida* JT103.[40] Furthermore, 2-trifluoromethylbenzoate is metabolised to its *ipso,ortho* diol by *Pseudomonas aeruginosa* 142[41] and metabolism of both 1-naphthoate and 2-naphthoate to their *ipso,ortho* diols is also known.[42] Dihydroxylation of terephthalic acid and isolation of the *ipso,ortho* diol has been disclosed in a patent.[43] Save for simple derivatisations to aid in their structural elucidation, or their deliberate dehydrative rearomatisation, no synthetic uses of these diols (Figure 7) have been reported. When the possibility of expanding the substrate scope of BZDO and other dioxygenases by directed evolution is considered, it is clear that there is great potential for arene *ipso,ortho* diols to continue to provide rapid access to uncharted chemical space.

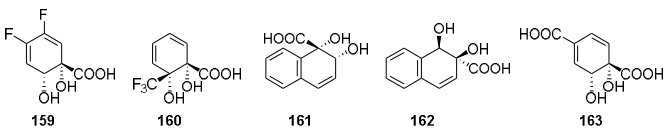


Figure 7. Arene *ipso,ortho* diols that have not been exploited synthetically.

Biography

Simon Lewis was appointed as a lecturer at the University of Bath in 2008. Since then he has pursued a research programme that encompasses microbial arene oxidation and other biotransformations. In addition, he has research interests in dye-sensitized solar cells, C-H functionalization with base metals, asymmetric catalysis and the chemistry of azulene. His work on the iron-mediated acetonide migration in an ipso,ortho diol derivative (Scheme 10) was published in the 2011 Chem. Commun. "Emerging Investigators" special issue.[20]

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